Articles

Ciguatera Fish Poisoning
A Southern California Epidemic

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Ciguatera fish poisoning results from the bioconcentration of a variety of toxins produced by marine dinoflagellates. Signs and symptoms vary widely, but it usually presents as gastrointestinal and neurologic complaints beginning shortly after the ingestion of fish containing the toxins. Symptoms may persist for months and sometimes even years. Although cases have been reported throughout the United States, epidemics are most common along tropical and subtropical coasts and usually involve the ingestion of large carnivorous fish. We review the literature and report the first epidemic of 25 cases of ciguatera fish poisoning presenting to area hospitals in Southern California that were successfully tracked by the Department of Health Services and isolated to fish caught off the coast of Baja California, Mexico.

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In the Evening every one who had eat some of these fish (called Groopers) were seiz'd with Violent pains in the head and Limbs, so as to be unable to stand, together with a kind of scorching heat all over the Skin (. . . and numness in the joints . . .), there remained no doubt but that it was occasioned by the fish being of Poisoness nature and communicated its bad effects to every one who had the ill luck to eat of it even to the Dogs and Hogs. [O]ne of the latter died in about Sixteen hours after and a young dog soon after shared the same fate. (It was a Week or ten days before all the gentlemen recover'd).

JOURNALS OF CAPTAIN JAMES COOK ON HIS VOYAGES OF DISCOVERY, JULY 1774[1]

Ciguatera toxins are tasteless, odorless, heat-stable, and lipid-soluble compounds originating in dinoflagellate eukaryotic organisms that attach themselves to marine algae thriving in tropical and subtropical reef systems.[2-4] A variety of compounds, including ciguatoxin, maitotoxin, scaritoxin, palytoxin, and possibly okadaic acid, are thought to be involved. These toxins are passed up the food chain from small plant-eating fish to large predatory fish, with increasing concentrations at each succession. Toxins are found in virtually every part of the fish, but appear to be more concentrated in the head, organs, and roe.[5] Most fish appear to be unaffected by ciguatera toxins, although the mechanism of resistance is unclear. These toxins, however, have proved poisonous to a variety of animals (including mammals), birds, reptiles, crustaceans, insects, and humans.[6]

Ciguatera fish poisoning is considered a world health problem, with outbreaks documented in numerous coastal countries. It is prevalent in the tropical Caribbean and the subtropical North Atlantic and Pacific regions. Cases are being recognized with increasing frequency in the United States.[5,7] Certain weather patterns and ecologic disturbances such as earthquakes, typhoons, and tidal waves or tsunamis are thought to be some of the natural causes of outbreaks of ciguatoxin. These disturbances to reef systems cause the toxic organisms, normally residing beneath the sand, to swim and spread.[4,5,8] Human activities such as shipwrecks, underwater or shoreline explosions, military activities, or the construction of docks and piers have also been implicated.[9]

We report an epidemic of 25 cases of ciguatera poisoning on the Pacific Coast of the United States as discovered and tracked by the Department of Health Services in San Diego, California, over a four-month period.

Report of Cases

Patients 1 through 4

In March 1992, a 47-year-old woman sought care early in the morning at a San Diego-area emergency department with nausea, vomiting, loose stools, and neurologic complaints, including paresthesias of the face, arms, and legs. She also had dizziness and shortness of breath and noted that her symptoms began after consuming fish for dinner the previous night. She appeared dehydrated, had bradycardia at 40 beats per minute, and was admitted to the hospital for observation. The woman's 50-year-old husband also became symptomatic later that day and presented to the hospital with the family's two daughters for evaluation.

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His symptoms included nausea, vomiting, and diarrhea, and he had tingling and numbness in his hands and feet. Their 14-year-old daughter experienced dizziness and a stomachache a few hours after eating, then vomited and had loose stools over the next 12 hours. She complained of tingling and numbness in her legs and fingers, feeling like they were "asleep." She also appeared dehydrated, with cool, moist skin and had difficulty walking. Her vital signs were normal. Her 16-year-old sibling reported similar symptoms, including the feeling that she could not move her legs and that her blankets were heavy on her legs. None of these patients had abnormal electrocardiograms or laboratory study results. Most of the gastrointestinal symptoms lasted less than 24 hours; all family members had persistent paresthesias and numbness in their extremities for several days after their fish meal, however.

The mother of the family reported that she had prepared a *lapo lapo* (a Filipino term for a grouper fish) for dinner on the night before the onset of symptoms. She had purchased the fish frozen from the garage of a private residence in the neighborhood. She prepared it by thawing, cleaning, and gutting it, then washed, breaded, and deep-fried the fish. She had also prepared and eaten a soup from the head of the fish. Environmental Health Services (EHS) staff from the Department of Public Health and from California Fish and Game investigated the garage where the fish was purchased and stopped any further sale of seafood from the facility. The owner admitted to selling the fish to the family and said that the fish was locally caught by a licensed commercial fisher; however, no information was given about the fishing boat or its owners. Frozen fish was impounded, along with the remains of the family's cooked fish, and sent to a laboratory in Hawaii to be tested for ciguatera toxin.

Patients 5 through 7

A few weeks after the first suspected group of poisonings, a local public health nurse informed the EHS of another family who had been seen in an area emergency department and diagnosed with ciguatera poisoning. Three of five family members had been treated with supportive measures including intravenous fluids for gastroenteritis, myalgias, chills, and paresthesias several hours after eating fish purchased from a local market. The two family members who were asymptomatic had not eaten the fish.

This time, EHS staff located the fisherman from the wholesale market where the fish had been bought. He reported that the implicated fish was a type of grouper called a cabrilla caught off the coast of Baja California, 468 miles southwest of San Diego and 235 miles off shore. He provided the name of the boat and information about its owners.

An interested researcher at Scripps Institute of Oceanography obtained a picture of the fish from the fisherman (Figure 1) and identified it as a flag cabrilla (*Epinephelus labriformias*, or red-tipped rock bass), a common channel water grouper that resembles the lapo

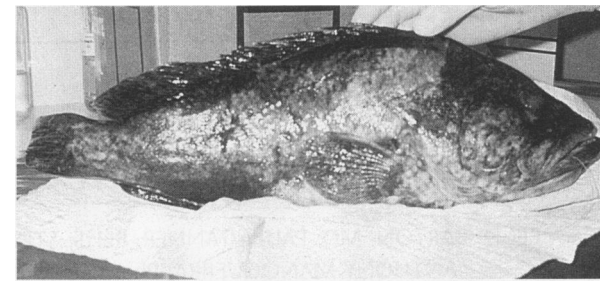

Figure 1.—The fish cabrilla (*Epinephelus labriformias*) is a channel water grouper found off the coast of Baja California, Mexico. This fish was one of the catch implicated in cases of ciguatera poisoning.

lapo grouper of the Philippines. This cabrilla is found off the coast of Baja, Mexico, south from Magdalena Bay and throughout the Gulf of California down to the coast of Peru. These particular fish were caught in the Alijos Rocks area off the Baja coast, 300 nautical miles west of Cabo San Lazaro, at a depth of 18 m (60 ft) (Figure 2).

Patients 8 through 24

In June 1992, three months after the initial outbreak of poisonings, a 66-year-old man came to another San Diego emergency department with vomiting, diarrhea, and neurologic symptoms about six hours after eating a fish that had been given to him by friends on a tuna seiner. His neurologic symptoms included sensitivity to cold, temperature reversal, paresthesias, difficulty walking, myalgias, and pruritus. He was treated supportively with histamine blockers, and his symptoms resolved over the next several days. The patient had made a stew of the entire 1.4-kg (3-lb) fish, including the head. He turned over a second smaller fish to EHS for testing.

The tuna seiner was identified within several days. All 16 crew members had been diagnosed with ciguatera poisoning by Memorial Maritime Medical Services. The physician involved said that the entire crew had temperature reversal, tingling of the palms and soles, and gastroenteritis and that one crew member had "cardiovascular

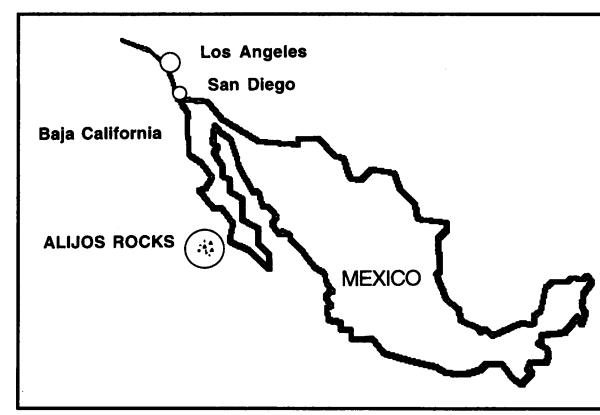

Figure 2.—The Alijos Rocks area, where the toxic fish was found, is located off the coast of Baja California, Mexico.

involvement," the nature of which was not specified. None of the crew needed to be admitted to a hospital, but blood specimens were taken from all involved and sent for testing. Crew members said that the cook on board the seiner had prepared a stew using the heads of fish caught on that trip. The location of this catch was at the coordinates of the Alijos Rocks area off the coast of Baja, corresponding exactly to the location of the previously involved catch. Frozen fish specimens were obtained and again identified as *E labriformias*, or flag cabrilla.

Patient 25

Several weeks later, a 42-year-old passenger from the same fishing expedition on the tuna seiner presented to a neurologist in San Diego with neurologic symptoms similar to those described for the crew, including night sweats and myalgias, that had persisted since the trip. He also stated that water felt cold on his hands and that he itched all over his body. He had also eaten the stew prepared on board from the fish heads. He had had 20 cabrilla in his freezer at home that he was preparing to ship to his relatives in New York, but had thrown them away after he became ill. His symptoms resolved over the next several months.

All fish and patient blood specimens were sent to the University of Hawaii, Manoa, where research is being done on ciguatera detection. Using a stick-enzyme immunoassay, a characteristic ciguatoxin-like compound was detected in the fish specimens. Ciguatera toxin levels in blood specimens from the affected persons were not able to be established when it was discovered that normal serum lipids interfered with the assay. Unfortunately, blood specimens were not retained for testing with more recently developed assays.

Discussion

Ciguatera has been an important cause of morbidity in the Caribbean and South Pacific, primarily in latitudes south of Hawaii. In the United States, cases have been reported from Florida, Louisiana, Massachusetts, New York, Vermont, District of Columbia, Texas, Kansas, Hawaii, Samoa, the Virgin Islands, and Puerto Rico.[5,7,10] Ciguatera is now endemic to Hawaii and Florida and found commonly in a variety of fish. More than 400 species of fish have been implicated in ciguatera outbreaks in one comprehensive report,[11(p63)] although more recent studies suggest that the actual number of infected species is low.[5] A total of 16 different fish were implicated in 172 cases of ciguatera in a recent series observed over a two-year period in Hawaii.[12] Ciguatera is not a new disease to US waters, being described as early as the 17th century. A number of cases have been recognized in nontropical areas of the inland United States, but most of these are attributed to fish imported from endemic areas.

Coral reef-dwelling and semipelagic fish are the actual vectors for the disease.[4] These large reef fish, including barracuda (*Sphyraena* species), grouper (*Epinephelus* and *Mycteroperca* species), red snapper (such as *Lutjanus* and *Sebastes* species), and amberjack (*Seriola* species), are caught near shorelines at depths of less than 91 m (300 ft). Ciguatera toxins are more concentrated in these species because they prey on smaller herbivorous fish that graze on macroalgae and detritus of coral reefs that contain the toxic dinoflagellates.[4,5] In addition, herbivore populations turn over quickly due to death or consumption and thus do not remain toxic for prolonged periods. Longer-living carnivorous species of fish at the higher end of the food chain may remain toxic for several years.

Outbreaks of ciguatera are thought to depend on a number of environmental factors. Water temperature, pH, and salinity may be important to the proliferation of toxic dinoflagellates.[13] *Gambierdiscus toxicus* is the predominant benthic dinoflagellate associated with ciguatera.[5] These organisms live on dead coral and thrive on a medium rich in algae, fungi, yeast, and bacteria. The presence of specific bacterias that synthesize the toxins after phagocytosis by the dinoflagellates is thought to be required for producing ciguatera toxin.[4]

Disturbances in coral reef environments by natural events such as storms, heavy rains, earthquakes, and tidal waves may precipitate outbreaks.[5,9] Toxic fish are often found on the windward side of tropical islands where wave energy and storm damage to reef systems is greatest. Human disturbances such as military activities in the Pacific islands, nuclear test explosions, construction, and shipping activities have also been shown to stimulate the proliferation of endemic ciguatera toxin.[9]

Epidemiologic physicians of the San Diego County Department of Public Health have suggested that the San Diego outbreak may have resulted from the unusual winter weather of 1991 and 1992, with several ocean storms and the El Niño phenomenon. The El Niño southern oscillation, which occurs approximately every ten years in an unpredictable pattern, causes widespread effects on the weather and water temperatures across the Pacific.[14-16] Profound changes have been observed in monsoon patterns, rainfall, agricultural production, and marine ecosystems during these oscillations. There is a rise in surface water temperature and even in mean sea level that results in a decline in marine productivity. The composition of phytoplankton species has been noted to change in the warmer waters of El Niño, with a predominance of zooplankton such as dinoflagellates.[14,15] An earlier study found a correlation between El Niño southern oscillation events and the proliferation of *Gonyaulax* species, the dinoflagellates responsible for paralytic shellfish poisons and cases of such poisonings in Washington State and British Columbia over a 40-year period.[16] Thus, such events might explain the sudden proliferation of *Gambierdiscus* dinoflagellates and the concomitant concentration of ciguatera toxins in flag cabrilla in coastal waters that were previously uninfected.

Although the cellular pathophysiology involving ciguatera remains unclear, several mechanisms of action have been suggested. The "opening" of sodium channels

in cell membranes through the occupation of calcium sites on these cells has been noted.[17] This could account for observed effects on action potentials in cardiac and neurologic tissue. Ciguatera toxin has also shown cholinergic as well as anticholinergic activity.[18] It is unclear, however, how other components such as maitotoxin and scaritoxin may contribute to the observed clinical effects.[19]

Diagnosis

The diagnosis of ciguatera is usually made by a history of fish ingestion followed by a typical combination of gastrointestinal, cardiovascular, and neurologic symptoms (Table 1). The onset of symptoms is similar to that of other food poisoning syndromes, often starting within 6 hours, with patients having nausea, vomiting, or diarrhea. Paresthesias of the extremities and numbness around the lips and tongue are common early symptoms and should alert a practitioner to ask about recent fish consumption. Almost all patients with notable exposures will seek care within 24 hours of ingestion.[4,5,7] Clinical presentations are highly variable and can be severe, including shock or coma. Eating the viscera, liver, or head of affected fish usually results in more serious poisonings because of the higher concentration of toxins in these tissues. One study reported mortality as high as 12%,[20] although actual mortality is probably lower.[21] Death is usually a result of cardiovascular or respiratory failure.

Cardiovascular effects associated with ciguatera are thought to result from a positive inotropic effect of the toxin on myocardium.[22] Dysrhythmias, including extrasystoles and bradycardia, and hypotension may occur in as many as a third of cases.[21] The treatment of shock may be required in some patients.

Neurologic complaints are almost pathognomonic to this disease and may persist for weeks to months, sometimes even years. Symptoms range from tingling or paresthesias to ataxia and lower extremity paresis.[4,5,7] Alterations in taste, myalgias and arthralgias, and fatigue are common symptoms. Temperature reversal is the most characteristic complaint and often manifests as cold objects feeling hot or burning to the touch. Other symptoms such as severe itching, photophobia, and psychiatric disturbances have been reported.[4]

A wide variation in the frequency and severity of symptoms has been noted.[12,23,24] These differences have been found to be associated with the type of fish eaten. The ingestion of herbivorous fish can result in exposure to more than one active ciguatera toxin.[23] Different species of carnivorous fish that feed on smaller herbivores may concentrate toxins differently. The dinoflagellate organism *G toxicus* elaborates both ciguatoxin and maitotoxin. Differences in biochemical alterations may promote other variants of toxins or active metabolites. Cardiovascular symptoms may occur more frequently in persons who eat carnivorous fish than in those who consume herbivores because of the increased toxin concentrations.[12] The patients in our series who ate the flag cabrilla primarily exhibited gastrointestinal and neurologic symptoms, although one woman did have bradycardia and hypotension.

TABLE 1.—*Symptoms of Ciguatera**

Symptom	Cases, %
Gastrointestinal	
Diarrhea	38-91
Vomiting	30-70
Nausea	33-44
Abdominal pain or cramping	35-43
Cardiovascular	
Bradycardia	9-37
Hypotension	10-25
Tachycardia	2-16
Musculoskeletal	
Arthralgias	33-86
Myalgias	30-85
Neurologic	
Extremity paresthesias	58-96
Circumoral or facial paresthesias	36-96
Temperature reversal	36-87
Asthenia	60-70
Headache	25-60
Pruritus	42-58
Paresis	10-33
Diaphoresis	18-29
Dizziness or vertigo	10-21
Ataxia	8-15
Dyspnea	8-12
Coma	8

*Adapted from Swift,[4] Kodama and Hokama,[12] Morris et al,[32] and Palafox et al.[37]

Ciguatera toxin has been associated with a variety of other disorders. One study reported the development of polymyositis in two persons after severe poisonings.[25] Ongoing research has shown ciguatera toxin-positive blood specimens in some persons previously diagnosed with the chronic fatigue syndrome, and in coastal cities, groups of patients with the chronic fatigue syndrome have a higher incidence of blood specimens positive for ciguatera toxins than patients with this syndrome who reside in midwestern cities (D.L. Parks, PhD, Nutrition and Food Science Dept, University of Arizona, oral communication, February 1994). Ciguatera toxin has been found in breast milk after acute exposure[26] and has been implicated in dyspareunia after possible sexual transmission.[27] Analysis of ciguatera toxins in blood specimens suggests that the toxin can be stored in adipose tissue for several years and that symptoms may recur during periods of stress such as exercise, weight loss, or excessive alcohol use (D.L. Parks, PhD, oral communication, February 1994).

The toxin is virtually impossible to detect in tissues or body fluid specimens without complex laboratory analysis. Mouse bioassays using extracts of fish tissues were reported in the early 1960s to determine the contamination of fish.[28] A direct radioimmunoassay was then developed using antibodies made in sheep and rabbits.[29] This

method allowed the testing of both fish specimens and human blood specimens for the presence of ciguatera toxins. Most recently, a rapid stick-enzyme immunoassay using horseradish and peroxidase-labeled sheep anti-ciguatera toxin antibody has been developed by Hawaii Chemtect International (Ciguatect) for detecting ciguatera toxins and toxins associated with diarrheic shellfish poisoning.[30] This test may soon be widely available to detect toxins in fish in only 15 minutes. Other products that will detect ciguatera toxins in human serum are also undergoing testing.

Treatment

The treatment of ciguatera poisoning has primarily been supportive. No known antitoxin is available. Previous treatments have been based on folk remedies and empiric drug therapy. Antiemetics, antidiarrheals, and intravenous rehydration are often necessary. Atropine sulfate has been used successfully for symptomatic bradycardia.[4,31,32] Intravenous calcium gluconate may have some theoretic benefit in counteracting the inhibition of calcium uptake by excitable membranes.[4,31] In addition, the use of magnesium-based cathartics should be avoided because of their possible calcium channel blocking action.[31] Pralidoxime chloride has been used as a cholinesterase reactivator based on laboratory data that ciguatera toxin acts as a cholinesterase inhibitor, although controlled studies have not been done.[32] Amitriptyline hydrochloride has been shown to provide variable relief for the neurologic symptoms associated with ciguatera poisoning, possibly related to a membrane-stabilizing effect through sodium channel blockade or through its anticholinergic activity.[33-35]

A study using intravenous mannitol reported an immediate resolution of most symptoms in 24 patients.[36] Mannitol, 0.5 to 1.0 grams per kg in a 20% solution given intravenously over a 10- to 30-minute period, is now considered the treatment of choice in both children and adults.[4,8,36-39] The mechanism of action of mannitol remains unclear, although it has been speculated to exert a membrane-stabilizing effect similar to that of amitriptyline.[36,37] No controlled studies have been done to confirm the efficacy of mannitol, and side effects such as dehydration can occur in some patients.[8,39] This risk is relatively low, however, and the immediate as well as the prolonged benefits of this treatment suggest that intravenous mannitol remains the preferred therapy at this time.

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